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Review

Primary bone marrow oedema syndromes

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Abstract

MRI scanning in patients with rheumatological conditions often shows bone marrow oedema, which can be secondary to inflammatory, degenerative, infective or malignant conditions but can also be primary. The latter condition is of uncertain aetiology and it is also uncertain whether it represents a stage in the progression to osteonecrosis in some patients. Patients with primary bone marrow oedema usually have lower limb pain, commonly the hip, knee, ankle or feet. The diagnosis is one of exclusion with the presence of typical MRI findings. Treatment is usually conservative and includes analgesics and staying off the affected limb. The natural history is that of gradual resolution of symptoms over a number of months. Evidence for medical treatment is limited, but open-label studies suggest bisphosphonates may help in the resolution of pain and improve radiological findings. Surgical decompression is usually used as a last resort.

Key words: bone marrow oedema, oedema, bone bruising, osteoporosis, regional, transient, MRI, bisphosphonates, iloprost, core decompression.

Introduction

The increasing use of MRI in rheumatological practice has led to the recognition of new findings where conventional X-rays rarely showed abnormalities. One example is bone marrow oedema, which is a common finding and can be seen in patients with inflammatory arthritis, inflammatory spondylitis, enthesitis [1, 2], OA [3], trauma and fracture [4], infections and cancers [5] or as an isolated finding [6, 7].

The term bone marrow oedema was first used by Wilson *et al*. in 1988 [8], who found ill-defined bone marrow hyperintensities on T2-weighted MR images in patients with knee and hip pain. They used this term because of 'the lack of a better term and to emphasize the generic character of the condition'. Thus, while MRI is sensitive for bone marrow oedema, it is a non-specific finding and it remains unclear whether the presence of bone marrow oedema in rheumatological conditions such as OA and RA are driven by the same pathological processes. Indeed, there is controversy about whether oedema is truly found in the bone marrow at these sites.

Where bone marrow oedema is found on MRI as an isolated finding without obvious cause, the term bone marrow oedema syndrome has been used by previous authors [6, 7]. Thus Thiryayi *et al*. [7] suggest that 'bone marrow oedema syndrome describes a clinico-radiological entity in which transient non-specific subacute or chronic joint pain, predominantly of the hip and knee, is associated with characteristic MR appearances in the absence of specific signs of avascular necrosis, antecedent trauma or infection'. In 1993 Solomon [6] suggested that 'it is important to recognize the difference between bone marrow oedema without osteonecrosis and that with osteonecrosis. The former is a hypervascular, usually self-limiting disorder, whereas the latter is unequivocally an ischaemic disorder which may go on to bone collapse and articular distortion'.

The purpose of this article is to review the bone marrow oedema syndromes from a clinical perspective with a focus on diagnosis and a review of the evidence for treatment. I will use the term primary bone marrow oedema syndrome to distinguish this clinical entity from secondary bone marrow oedema associated with the diseases listed above. PubMed was searched through to January 2013 for relevant articles using multiple search terms including bone marrow oedema, bone oedema, regional osteoporosis, transient osteoporosis and migratory osteoporosis. Variations as shown in Table 1 were also used. Citations from the identified articles were used to obtain additional relevant references. Only English language articles were considered.

Aetiology

The aetiology of primary bone marrow oedema remains uncertain. It has been suggested that a local ischaemic

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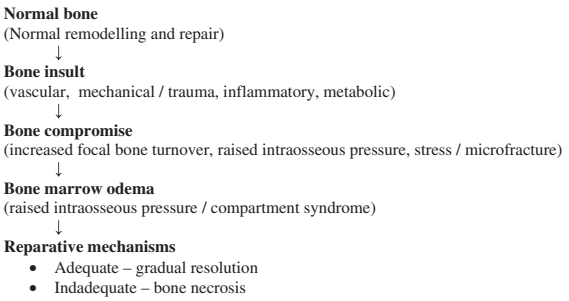
Table 1 List of various terms found in the literature

Acute bone marrow oedema
Bone bruising
Bone marrow lesions
Bone marrow oedema syndrome(s)
Oedema-like bone marrow abnormalities
Migratory transient osteoporosis
Post-transplant distal limb syndrome
Regional migratory osteoporosis
Regional transient osteoporosis
Shifting bone marrow (oedema of the knee)
Transient bone marrow oedema syndrome
Transient osteoporosis
Transient migratory osteoporosis
Transient bone marrow oedema

From references [5, 9, 10, 13–24].

Fig. 1 Hypothetical aetiological pathway of bone marrow oedema and osteonecrosis



Adapted from references [10, 11].

episode, due to multiple triggers, may initiate a chain of events resulting in bone marrow oedema [9–11]. However, the evidence is at best limited and inferred from histological findings suggesting abnormal vascularity, oedema and increased focal bone turnover.

It also remains unclear whether primary bone marrow oedema syndrome is a separate entity from or represents an early stage of osteonecrosis. That is, are these individual distinct conditions or is this is a single disease with differing findings on clinical and radiological sampling during the natural history of the condition, where in some patients repair mechanisms avoid progression to bone death? Thus, are bone marrow oedema syndromes a distinct transient disease or an early potentially reversible stage of the course of osteonecrosis sharing a common developmental pathway? A potential sequence of events is shown in Fig. 1. The distinction between bone marrow oedema and osteonecrosis is important to judge clinically and radiologically, as osteonecrosis usually requires surgical intervention, whereas primary bone marrow oedema syndrome generally is best managed conservatively [12]. A recent review highlights drugs that may contribute to osteonecrosis (e.g. thiazolidinediones, serotonin reuptake inhibitors, NSAIDs and HIV protease inhibitors), therefore these agents are best avoided in patients with primary bone marrow oedema syndromes [13].

The pathophysiology of pain in bone marrow oedema syndromes is poorly understood and thought to be multifactorial. Thus increased intraosseous pressure, with irritation or disruption of sensory nerves within the bone marrow, venous hypertension, raised focal bone turnover with or without microfractures and irritation of the periosteum and periarticular structures could all be possible mechanisms [14, 15].

Nomenclature

The complexity of bone marrow oedema syndromes is compounded by the use of different terminologies due to changing perceptions of the conditions with time and by different specialities within medicine (radiology *vs* clinicians, orthopaedics *vs* rheumatology). These inconsistencies have led to controversy in pathological, radiological and clinical classifications and hence contributed to uncertainties about management.

Initial terminology focussed on bone or tissue death (osteonecrosis), avascularity (avascular necrosis), findings of osteoporosis on plain X-rays that was confined to one part of the skeleton (regional osteoporosis) and which in some patients was self-limiting (transient), although it could spread to involve other bones (migratory) or move within the same bone (shifting). With the advent of MRI, the radiological term bone marrow oedema is used, as the signal changes in the bone marrow suggest increased water content and therefore oedema. In addition, in the orthopaedic literature, as these lesions are seen after trauma (often mild), the term bone bruising has been used [4]. Within the OA research community the term bone marrow lesions is used to describe the MRI findings [16]. Table 1 lists various terms used in the literature when bone marrow oedema is found.

Classification

The classification of bone marrow oedema remains rather arbitrary given our poor understanding of the disease process. Table 2 lists an adapted classification according to putative risk factors. It is important to stress that primary bone marrow oedema syndrome should only be diagnosed once other causes of both the clinical and radiological findings have been excluded. The list of causes of secondary bone marrow oedema syndrome in Table 2 overlaps with causes of osteonecrosis in the literature and contributes to the confusion and uncertainty as to whether they are distinct entities or different stages of the same condition. Moreover, there is uncertainty about the differences between primary bone marrow oedema and that due to secondary causes in terms of natural history and imaging findings that requires further study.

Table 2 Classification of bone marrow oedema

Primary
Bone marrow oedema syndrome without an identifiable underlying cause
Secondary
Trauma (direct injury, ligamentous damage, complex regional pain syndromes, fracture)
Degenerative (e.g. OA)
Inflammatory (e.g. inflammatory arthritis, enthesitis)
Ischaemic (e.g. sickle cell disease, polycythaemia)
Infectious (e.g. septic arthritis, osteomyelitis)
Neoplastic (primary or secondary bone cancers, benign lesions such as osteoid osteomas)
Iatrogenic (e.g. after surgery or radiotherapy, drugs such as steroids or calcineurin inhibitors)
Metabolic (e.g. chronic kidney disease and its treatment)
Neurological (Charcot's joints)

Adapted from references [22, 23].

Imaging

Unlike imaging modalities such as plain X-rays, CT or US, MRI scanning is unique in that it uses the presence of protons to generate images. These protons are usually in water molecules and the presence of an MRI signal suggestive of excess protons/water in bone marrow gives rise to the term bone marrow oedema. Normal marrow signal on MRI parallels that of subcutaneous fat, being high on conventional T1-weighted imaging and intermediate to low on T2-weighted fat-suppressed imaging.

As a result of increased water content within the marrow, bone marrow oedema gives an intermediate signal on T1-weighted images (higher than muscle or intervertebral disc) and a high signal on T2-weighted images. On contrast-enhanced and short-tau inversion recovery (STIR) imaging bone marrow oedema appears hyperintense compared with normal bone marrow [8, 15]. Other important bone marrow oedema characteristics include these findings being relatively homogeneous and having indistinct margins at the interface with normal marrow (Fig. 2). MRI may also demonstrate an irregular band of low signal intensity on all sequences that may be interpreted as a stress fracture [15]. Whether a stress fracture is the cause of the bone marrow oedema or a consequence of bone marrow oedema remains controversial. Increased focal bone turnover may result in increased numbers of stress risers within trabeculae that cause microdamage and lead to stress fractures.

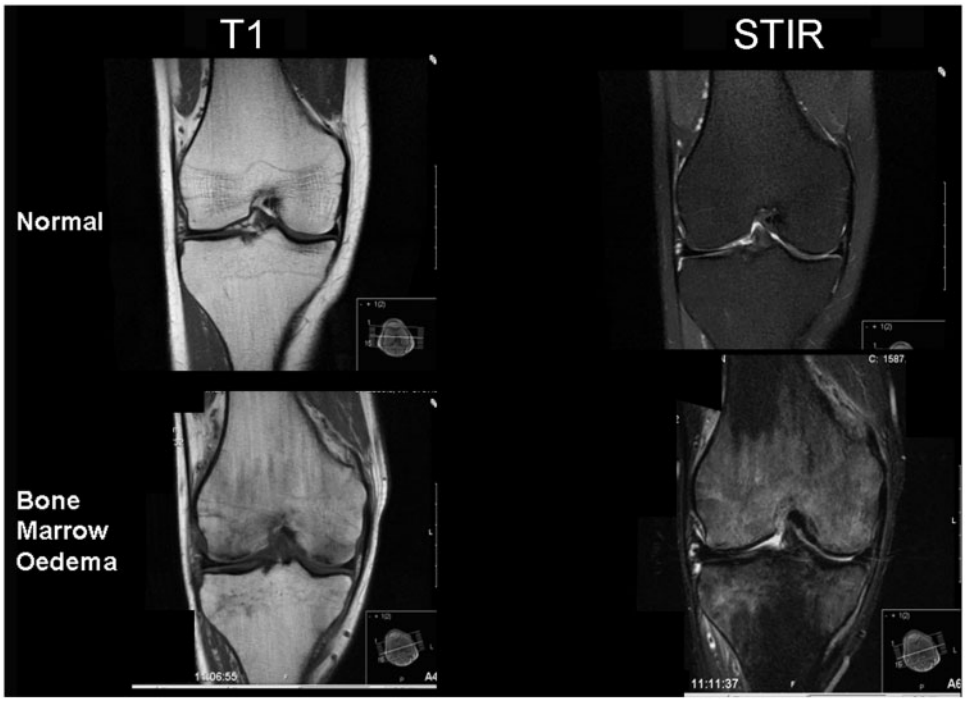
Where there is uncertainty about an underlying cause of the MRI changes, other imaging modalities such as plain X-rays, CT scanning and isotope bone scanning should be considered [14]. Plain X-rays of the painful area are usually done by the time a patient is referred to a rheumatologist. Plain X-rays complement MRI and may help to exclude other obvious pathologies that may be causing the bone marrow oedema. Reduced regional bone density (regional osteoporosis) on plain X-rays is usually a late feature of bone marrow oedema syndromes and may persist for some time after the resolution of symptoms [22]. CT scanning cannot detect bone marrow oedema but may be helpful to exclude focal bone lesions such as osteoid osteomas. Isotope bone scanning has a limited role if MRI is available, but has the advantage of being able to evaluate both the site of symptoms as well as other parts of the skeleton in selected patients to exclude metastatic cancers.

Clinical features of primary bone marrow oedema syndromes

No adequate epidemiological studies have been performed to date. It is likely that mild cases settle spontaneously and may never reach medical attention. Primary bone marrow oedema syndromes most commonly affect the hip, followed by the knee, ankle and foot, although this is based on case reporting as opposed to epidemiological data. Underreporting and underrecognition is likely to be common. However, it is clear that the syndrome rarely affects the upper extremity and is rare in children. The classical association is with pregnancy (usually in the third trimester). Case series of men with the condition suggest that the most common age of onset is between 40 and 60 years of age. It has been suggested that the condition is more common in patients with osteogenesis imperfecta [25–28], although whether this is a chance finding is uncertain, as is whether outcomes differ, compared with patients without osteogenesis imperfecta.

The diagnosis is usually made in patients who present with musculoskeletal pain. This pain is usually of spontaneous onset and exacerbated by weight bearing if the lower limbs are involved. The rate of onset of pain is variable, ranging from being vague and insidious in onset to a rapidly progressive severe pain that can cause immobility and require hospitalization. One or more skeletal sites can be involved and the symptoms are usually localized to one or more joints. A trivial or small effusion can be found where peripheral joints such as the knee, ankle or foot are involved. Trophic or vasomotor changes are usually absent. The joint is usually irritable. Percussion of the affected bone has been reported as being more painful than the normal contralateral side at the knee [29]. Subcutaneous oedema may be noted where the ankle

Fig. 2 T1 and STIR MRI coronal images of a normal knee and similar sequences in a patient with primary bone marrow oedema syndrome



and foot are involved. A key clinical feature is that the symptoms and disability are out of proportion to the clinical findings. I have found that irritability and pain on tapping the symptomatic bone (where possible), as suggested by Aigner *et al.* [29], is a useful clue to the condition.

Primary bone marrow oedema syndrome should be considered a diagnosis of exclusion in patients who have the clinical and radiological characteristics described above. In addition to excluding an active arthritis, it is vital to exclude a primary or secondary malignancy as well as benign bone lesions, which can be painful and associated with bone marrow oedema, such as an osteoid osteoma [30]. Complementary imaging to MRI, such as CT scanning, should be considered if there is doubt, as well as interval scanning, particularly if symptoms persist despite treatment.

The duration of symptoms is variable and depends on both the initial severity and extent of bony involvement and treatment. Symptoms may last from weeks to months. Typically the initial phase consists of severe pain with functional impairment gradually associated with bone loss on plain X-rays over a number of months followed by spontaneous resolution with improvement in bone density. Most series suggest that it takes 3–6 months for resolution of symptoms, although in some patients the condition may last longer [10, 31]. This will depend on the severity of the initial presentation and whether specific treatment is given. In some patients another bone may become involved in the same region (e.g. another bone within the foot) or a more distant bone in either the same limb or the contralateral limb [17, 32]. In the past the term regional migratory osteoporosis was used to describe this phenomenon. Recurrence months to years after the initial episode has settled is well reported and is often at another skeletal site, hence the term regional migratory osteoporosis, which was first described by Duncan *et al*. [33]. No specific laboratory tests aid in the diagnosis. Specific clinical scenarios are explored later in this article.

Histology

As bone marrow oedema syndromes are generally self-limiting, there are considerable difficulties in trying to compare radiological appearance with histological findings at the same site [7]. Thus histological sampling tends to be opportunistic with only a small number of studies in the literature. Moreover, samples may be unrepresentative of early or more benign or spontaneously improving individuals, and there may be inconsistencies in histological techniques.

A prospective study of 31 patients with bone marrow oedema of the hip (without radiological evidence of osteonecrosis) treated with core decompression within 3 weeks of diagnosis found high intramedullary pressures and a variety of histological findings [34]. These included evidence for abundant new bone formation, which the

authors suggested was part of a reparative mechanism, and changes thought to be due to diffuse interstitial oedema and dilation of medullary sinuses adjacent to bone surfaces. The latter findings were interpreted as the histomorphologic substrate of the bone marrow oedema pattern in MRI. A recent review of histological findings was published by Thiryayai *et al*. [7].

Bone density measurements

Although some reports have shown that patients with bone marrow oedema may have osteoporosis or osteopenia, it remains uncertain as to whether patients with osteoporosis are at higher risk of bone marrow oedema, as patient numbers were small and without controls [10, 15].

DXA has been used to follow changes in hip bone density in patients with a diagnosis of transient osteoporosis of the hip. Funk *et al*. [35] reported post-delivery increases in femoral neck bone density in a woman with transient osteoporosis of the hip diagnosed during pregnancy, from a baseline *Z*-score of −1.8 to −0.5 (an increase of +1.3 S.D.) over a period of 4 years. Similar large increases in femoral neck bone density were reported in three patients with spontaneously improving transient osteoporosis of the hip [36].

Biochemical markers of bone turnover

Systemic and focal bone turnover were explored in a study of 37 consecutive patients with bone marrow oedema syndrome of the hip [9]. Markers of bone formation and bone resorption in peripheral blood were not elevated compared with controls, however, they were elevated in aspirate samples taken from the site of bone marrow oedema. These findings suggest that the focal reduction in bone density seen at sites of bone marrow oedema is due to localized increases in bone turnover.

Specific clinical scenarios

Hip

Bone marrow oedema of the hip was first reported during pregnancy in three women by Curtis and Kincaid in 1959 [37], who used the term transient osteoporosis of the hip, as they only had plain X-rays to image the hips. These patients had a self-limiting course, which occurs in most patients with a time course of 3–6 months. Rarely spontaneous hip fracture can occur [38]. Involvement of the contralateral hip has also been reported as the initial hip recovers [21]. The condition is more appropriately called bone marrow oedema of the proximal femur, as the femoral head and neck is involved, with less frequent involvement of the trochanter and the acetabulum tending not to be affected. Risk factors other than pregnancy include excess alcohol consumption and steroid use and hypothyroidism [39], although no comparative studies have been performed to evaluate the magnitude of the risk.

Knee

The knee is also a common site for primary bone marrow oedema syndrome. As discussed above, pain is usually out of proportion to the clinical findings with a normal examination other than a trivial effusion. The knee may be irritable and the tapping test may be positive over the affected femoral condyle [29]. Symptoms may persist for months. Risk factors are similar to those for hip involvement. The bone marrow oedema is usually seen in the femoral condyles, with less frequent involvement of the tibia. The bone marrow may also shift from one condyle to another over the course of the condition [40]. A recent cross-sectional study suggests that age, low BMD and gender may influence the outcome of acute bone marrow oedema of the knee, although whether these variables are independent of each other is uncertain [41].

Ankle and foot

The ankle and foot are less commonly involved compared with the hip and knee. Soft tissue oedema is a common finding, possibly due to the bony structures being relatively superficial. Because of associated soft tissue swelling and oedema, the differential diagnosis needs to include inflammatory arthritides and sometimes cellulites (where there is overlying erythema).

Solid organ transplantation

Lower limb musculoskeletal pain due to bone marrow oedema syndrome has been reported as being common after solid organ transplantation [11], and is often associated with calcineurin inhibitors such as ciclosporin. This was first described by Bouteiller *et al*. [42], and subsequently Grotz *et al*. [43] termed this phenomenon the calcineurin inhibitor pain syndrome. The condition has been reported with other calcineurin inhibitors such as tacrolimus [44]. Symptoms may start from 1 to 6 months post-transplantation [45, 46] and characteristically involve multiple skeletal sites. A pre-symptomatic increase in serum total alkaline phosphatase that persists during and after remission of symptoms has been reported in patients after kidney transplantation [24, 46].

Pregnancy

Curtis and Kincaid [37] reported the association between transient osteoporosis of the hip and pregnancy. Subsequent reports have highlighted that this bone marrow oedema syndrome tends to occur in the third trimester, although the incidence remains uncertain. Bilateral hip involvement has been reported, as has involvement of other skeletal sites, such as the knee. A report of two pregnant patients who developed hip pain during pregnancy and were diagnosed with transient osteoporosis of the hip and were followed up for 10 years showed that they had low radial bone density at presentation and that this persisted for the duration of the follow-up [47]. The authors suggest that osteopenia existed prior to pregnancy.

Treatment

Initial treatment is conservative and consists of avoidance of weight bearing and immobilization of the affected area. Pain control is essential, and in some patients opiates may be required.

A variety of pharmacological treatments have been used, although randomized controlled trials are lacking. Drugs that have been reported as being helpful include glucocorticosteroids, bisphosphonates, calcium channel blockers and prostaglandin inhibitors (such as iloprost). Surgical core decompression is usually used as the last resort, particularly as the condition is self-limiting in the majority of patients. The primary objective of intervention is to reduce the duration of pain and disability and to avoid progression to bone failure or bone death (osteonecrosis). Concerns remain about positive reporting bias and a lack of controlled studies.

Bisphosphonates

The bisphosphonates, which are bone active drugs that are primarily anti-resorptive and reduce bone turnover, seem a reasonable choice of agent give the evidence for increased focal bone turnover at sites of bone marrow oedema lesions as described above. Moreover, bisphosphonate uptake is predominantly at sites of active turnover, thus in theory ensuring concentrated drug delivery at the site of the bone marrow oedema.

Reported studies of bisphosphonates have been limited by being open label and uncontrolled. Pamidronate has been the most commonly reported bisphosphonate used in this condition, which probably reflects its longer availability and intravenous route of administration [48]. Improvements in pain, MRI findings and bone density have been reported after a single infusion of pamidronate in patients with bone marrow oedema [23, 49]. In addition, alendronate [50, 51], clodronate [52], ibandronate [53, 54] and zoledronate [55] have been reported as being efficacious. In the case of alendronate and zoledronate, the doses used were similar to those for the treatment of post-menopausal osteoporosis.

Iloprost

The prostacyclin analogue iloprost has been used to improve tissue blood supply in a variety of situations through multiple mechanisms, including vasodilatation and inhibition of platelet aggregation. As ischemia may be important in the aetiology of bone marrow oedema syndromes, iloprost has been studied in patients with lower limb bone marrow oedema. Three small uncontrolled studies have reported the use of intravenous iloprost in patients with bone marrow oedema of the proximal femur [56], of the talus [57] and post-transplant lower bone marrow oedema [24]. All showed improvements in pain and MRI scans. A larger recent study of 61 patients showed similar findings [58]. A randomized controlled study of 41 patients examining oral iloprost *vs* oral tramadol in the management of bone marrow oedema of the knee [59] found that the analgesic effect of oral iloprost was similar to tramadol, although bone marrow oedema regression on MRIs was more pronounced in the iloprost group.

Other medical treatments

A randomized uncontrolled study of 41 patients with bone marrow oedema syndrome of the proximal femur treated with hyperbaric oxygen [60] reported significantly greater improvements in pain and MRIs with hyperbaric oxygen. There is one case report of teriparatide being used for the treatment of transient osteoporosis of the hip [61]. Calcium channel blockers have been used in post-transplantation bone marrow oedema syndrome with inconsistent benefit [46].

Surgical decompression

Surgical intervention for osteonecrosis, particularly core decompression of the femoral head, is widely reported [62], but there are fewer articles concerning patients with bone marrow oedema syndromes. This is because experience has demonstrated symptomatic and MRI improvement without surgery in patients with bone marrow oedema, as well as differences in opinion as to whether the condition is truly self-limiting or a potentially progressive condition resulting in osteonecrosis and where early surgical intervention will limit this progression. Most reports are case series with small numbers and usually without randomization of surgical intervention or an adequate control group [17, 19, 63, 64]. Thus the limited data for core decompression for the treatment of bone marrow oedema syndromes suggests that core decompression may reduce pain quicker than conservative treatment. What is uncertain is whether the natural history of the condition is changed and whether longer-term outcomes are better with surgery. Therefore core decompression is probably best reserved for patients with severe pain that is difficult to control.

Management recommendations

It is difficult to provide evidence-based guidelines, as the data are limited. Reporting bias needs to be taken into consideration, as patients with a poorer response may not be reported.

However, the following strategy should be considered. A low threshold is needed for considering the diagnosis, and appropriate investigations, including MRI scanning, should be performed to confirm the diagnosis and exclude other pathologies. A general medical evaluation and bone health evaluation, including bone density measurements, would seem sensible. Appropriate intervention such as smoking cessation, moderation of alcohol intake, optimizing calcium intake and correction of vitamin D deficiency should be advised. Analgesia should be tailored to the severity of the patient's symptoms and may in some cases justify opiates. Staying off the affected site by avoiding weight bearing with crutches and immobilization of the affected region is critical. Consideration should be given to pharmacological treatment in patients after appropriate explanation and consent for off-label drug use.

The use and timing of intervention will be very much dictated by the severity of the patient's symptoms and the clinician's experience and preference, given the lack of clinical data. It is the author's preference to use intravenous bisphosphonates such as pamidronate (60–90 mg) or zoledronate (5 mg), ensuring adequate levels of baseline vitamin D. Repeated evaluation to assess response and vigilance to ensure that there is not an alternative explanation for the patient's symptoms and findings are needed. Repeat imaging may be performed in patients who respond poorly to see if there has been progression to osteonecrosis, and while interval MRI can be performed, CT scanning may also be helpful. Surgical intervention should be considered in patients where conservative treatment fails, although there is limited evidence on when to intervene.

Rheumatology key messages

- Bone marrow oedema is a common finding on MRI scans.
- Lower limb joint pain in the absence of synovitis may be due to primary bone marrow oedema.

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